

Historical note**Diabetic retinopathy: An historical assessment**

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Diabetic retinopathy is a microvascular complication of diabetes mellitus and is a significant cause of new-onset blindness. Diabetic macular changes in the form of yellowish spots and full or partial thickness extravasations through the retina were observed for the first time by Eduard Jøger. In 1855, he published “Beitrøge zur Pathologie des Auges” where he included his fundus paintings. Jaeger’s findings were controversial until 1872, when Edward Nettleship published his seminal paper on “Oedema or cystic disease of the retina”, providing the first histopathological proof of “cystoid degeneration of the macula” in patients with diabetes. In 1876, Wilhelm Manz described the proliferative changes occurring in diabetic retinopathy and the importance of tractional retinal detachments and vitreous haemorrhages. However, it was not until 1943 that the work of Arthur James Ballantyne provided evidence that diabetic retinopathy represents a unique form of vascular disease. A number of multi-centred clinical trials during the last ten years have contributed substantially to the understanding of the natural history of diabetic retinopathy and have established the value of intensive glycaemic control in reducing both the risk of onset and the progression of diabetic retinopathy.

Key words: Diabetes mellitus, Diabetic retinopathy, Eduard Jäger, Vasculopathy

INTRODUCTION

The term diabetes was introduced by Aretaeus of Cappadocia, an eminent physician of the Pneumatic School, who lived in Alexandria and Rome during the 2nd century AD. He was a humoralist and was inspired by the Hippocratic ideas. He used the Greek verb διαβαίνω (diabaino = pass through) to define the condition where a large quantity of urine passes through {διαβαίνει (diabainei) = passes through} the kidneys.¹ Diabetes was identified as

polyuria following consumption of large amounts of drinking water, broadly accepted by all physicians as a symptom of renal dysfunction, and classified among diseases affecting the kidneys.

PRECURSORS OF DIABETIC RETINOPATHY

Although diabetes was a well-known disease since the 2nd century AD, no clinician attempted to link this endocrine disorder with eye-pathology before the middle of the 19th century. In 1846, the French ophthalmologist and Professor of Hygiene in Paris, Appolinaire Bouchardat (1806-1886) reported the development of visual loss in the absence of cataract in diabetics. This was partly reversible and in most cases improvement was associated with

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better control of diabetes.² A few years later, François Tavnignot made similar observations.³ However, no histopathological specimens were examined and the implication of macular disease in diabetes remained tentative until the invention of the ophthalmoscope.

THE RECOGNITION OF DIABETIC MACULOPATHY

Even though the first ophthalmoscope was introduced by Herman von Helmholtz in 1851, the newly invented instrument was still too complicated and the required training was too time-consuming to render examination of the ocular fundus an easy matter.⁴ It was Eduard Jøger (1818-1884) who constructed an instrument integrating in one apparatus the principles of Helmholtz's, Ruete's and other ophthalmoscopes,⁵ and, using this instrument, Jøger was the first to observe diabetic macular changes in 1855.⁶ Jøger had inexhaustible patience and exemplary precision in ophthalmoscopy, and in illustrating his findings, meticulously incorporated the smallest details into his pictures. He used the newly developed direct ophthalmoscope in order to produce one of the first atlases containing 21 colour plates of fundus paintings, which were drawn after 20-40 clinical sessions per patient.⁷ He described 'roundish' or oval, yellowish spots and full or partial thickness extravasations through the retina in the macular region of a diabetic patient.⁸ His findings were controversial at the time and Albrecht von Graefe (1828-1870) claimed that there was no proof of a cause-effect relationship between diabetes and retinal complications.⁹ Von Graefe's scepticism was adopted by many of his colleagues, with the exception of Louis Desmarres (1810-1882) in 1858.¹⁰

No further evidence was presented until 1869, when Henry Noyes (1832-1900) published an article in the USA supporting the link between diabetes mellitus and maculopathy.¹¹ His observations were confirmed in 1872 by Edward Nettleship (1845-1913) in London, who expanded on this theme in his paper entitled 'On oedema or cystic disease of the retina' and presented the first histopathological proof of a cystoid degeneration of the macula in diabetic patients.¹² Five years later, Nettleship pub-

lished another article with Sir Steven Mackenzie (1791-1868), which described in detail the abnormal retinal changes induced by diabetes.¹³

THE DISCOVERY OF PROLIFERATIVE DIABETIC RETINOPATHY

In 1876, Wilhelm Manz (1833-1911) published his seminal paper on 'Retinitis proliferans' containing several drawings of fibrovascular degeneration of the optic disc and vitreoretinal adhesions in the retina.¹⁴ Fourteen years later, in 1890, Julius Hirschberg (1843-1925) classified diabetic retinopathy into four types (retinitis centralis punctuate, haemorrhagic form, retinal infarction and haemorrhagic glaucoma), thus describing the full natural history of diabetic retinopathy.¹⁵ The descriptive term, diabetic retinitis, though erroneous since the disease is not of inflammatory origin, continued to be used for several years.

At the beginning of the 20th century there was still the unresolved debate as to whether macular changes were directly related to diabetes or whether they were caused by atherosclerosis and hypertension. Arthur James Ballantyne (1876-1954) of Glasgow suggested that diabetic retinopathy represents a unique form of vasculopathy and his work showed for the first time the role of capillary wall alterations in the development of diabetic retinopathy, as well as the presence of deep waxy exudates in the outer plexiform layer.¹⁶

Today the retinal manifestations of diabetes are classified as Early Non-proliferative Diabetic Retinopathy, Advanced Non-proliferative Diabetic Retinopathy and Proliferative Diabetic Retinopathy.¹⁷

THE EVOLUTION OF THERAPEUTIC MODALITIES FOR DIABETIC RETINOPATHY

In 1921, Frederick Banting (1891-1941) and Charles Best (1899-1978) extracted insulin from the pancreas, an achievement which is considered as one of the most significant contributions to endocrinology.¹⁸ Over subsequent decades, various types of injectable long-acting insulin preparations were introduced for the treatment of diabetes, and other

chemical agents were synthesized for oral administration to lower blood sugar,¹⁹ which, in conjunction with other measures, improved diabetes control and helped in the prevention of ocular complications.

The German ophthalmologist Gerhard Meyer-Schwickerath (1920-1992) began looking for a way to use light to purposely coagulate retinal tissue after seeing the effects of a solar eclipse on the retina of a student. In 1950, he reported treatment of retinal disorders with photocoagulation.²⁰ The clinical application of this invention for diabetic retinopathy was carried out in 1963 by Paul Wetzig and his colleagues.²¹ Charles Campbell and Christian Zweng were the first to use the ruby laser in a clinical setting, but it was William Beetham and Lloyd Aiello who recognized the effectiveness of photocoagulation in diabetic neovascular retinopathy.⁸ In 1979, the Diabetic Retinopathy Study Research Group proved that both xenon arc and argon laser panretinal photocoagulation (PRP) significantly decrease the possibility of severe visual loss.²² It is noteworthy that the exact mechanism by which PRP works remains unknown. In 1995, the Early Treatment Diabetic Retinopathy study Research Group (ETDRS) confirmed the results of Patz who had demonstrated in 1976 that argon laser photocoagulation decreases or stabilizes macular oedema.^{23,24}

Although medical treatment of diabetic retinopathy progressed during the 1950's and 60's, surgical treatment remained experimental through these two decades. In 1953, Poulsen observed that progression of proliferative diabetic retinopathy was decelerated in a woman who developed post-partum pituitary necrosis (Simmonds' disease). Empirical trials of pituitary ablation were attempted as treatment for severe retinopathy.²⁵ Hypophysectomy was effective in 30% of patients suffering from proliferative retinopathy, but because of the traumatic nature of the operation and the requirement of post-operative hormone replacement therapy, the procedure was replaced by laser treatment. Robert Macherer (1933-), who was the first to establish an experimental model of retinal detachment, is best known for his development of pars plana vitrectomy for the treatment of vitreous haemorrhages in proliferative diabetic retinopathy.²⁶

CONCLUSION

The prognosis of diabetic retinopathy used to be gloomy. Today it is broadly accepted that diabetic retinopathy is a microvascular complication of diabetes mellitus and a significant cause of new-onset blindness. Severe and moderate vision loss from diabetes is essentially preventable with early detection and treatment, careful long-term follow-up and comprehensive care by a multidisciplinary team of healthcare professionals. Several multi-centered clinical trials during the last ten years, and especially the Diabetic Control and Complications Trial (DCCT),²⁷ have significantly contributed to the understanding of the natural history of diabetic retinopathy and have established that strict glycaemic control reduces both the risk of onset and the progression of diabetic retinopathy and other microvascular complications of diabetes. Thus, future treatments, as outgrowths of further understanding of the biochemical basis of the disease, will aim at curing or preventing retinal complications from diabetes.

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